

We claim:

1. A method for the treatment or prevention of the symptoms or effects of an HIV infection in an infected animal which comprises administering to said animal a therapeutically effective amount of a combination comprising 9-[*R*-2-[(*S*)-[[(*S*)-1-(isopropoxycarbonyl)ethyl]amino]-phenoxyphosphinyl]methoxy]propyl]adenine (GS-7340) or a physiologically functional derivative thereof, and (2*R*,5*S*,*cis*)-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1*H*)-pyrimidin-2-one (emtricitabine) or a physiologically functional derivative thereof.

10 2. The method according to claim 1 wherein the combination comprises GS-7340 and emtricitabine.

3. The method according to claim 2 wherein the combination comprises about 150 mg of GS-7340 and about 200 mg of emtricitabine.

15 4. The method according to claim 1 wherein GS-7340 or a physiologically functional derivative thereof and emtricitabine or a physiologically functional derivative thereof are present in a ratio of about 1:50 to about 50:1 by weight.

5. The method according to claim 1 wherein GS-7340 or a physiologically functional derivative thereof and emtricitabine or a physiologically functional derivative thereof are present in a ratio of about 1:10 to about 10:1 by weight.

20 6. The method according to claim 1 wherein GS-7340 or a physiologically functional derivative thereof and emtricitabine or a physiologically functional derivative thereof are each present in an amount from about 1 mg to about 1000 mg per unit dosage form.

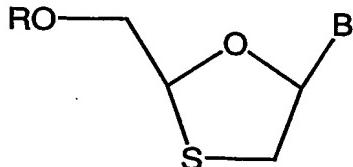
25 7. The method according to claim 1 wherein GS-7340 or a physiologically functional derivative thereof and emtricitabine or a physiologically functional derivative thereof are each present in an amount from about 100 mg to about 300 mg per unit dosage form.

8. A method according to claim 1 wherein GS-7340 is a fumarate salt.

30 9. A method for the treatment or prevention of the symptoms or effects of an HIV infection in an infected animal which comprises administering to said animal a

therapeutically effective amount of a combination comprising 9-[*R*-2-[[*(S)*-[(*S*)-1-(isopropoxycarbonyl)ethyl]amino]-phenoxyphosphinyl]methoxy]propyl]adenine (GS-7340) or a physiologically functional derivative thereof, and a compound of the formula:

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wherein B is selected from adenine, guanine, cytosine, uracil, thymine, 7-deazaadenine, 7-deazaguanine, 7-deaza-8-azaguanine, 7-deaza-8-azaadenine, inosine, nebularine, nitropyrrole, nitroindole, 2-aminopurine, 2-amino-6-chloropurine, 2,6-diaminopurine, hypoxanthine, pseudouridine, 5-fluorocytosine, 5-chlorocytosine, 5-bromocytosine, 5-iodocytosine, pseudocytosine, pseudoisocytosine, 5-propynylcytosine, isocytosine, isoguanine, 7-deazaguanine, 2-thiopyrimidine, 6-thioguanine, 4-thiothymine, 4-thiouracil, *O*⁶-methylguanine, *N*⁶-methyladenine, *O*⁴-methylthymine, 5,6-dihydrothymine, 5,6-dihydrouracil, 4-methylindole, and a pyrazolo[3,4-D]pyrimidine; and

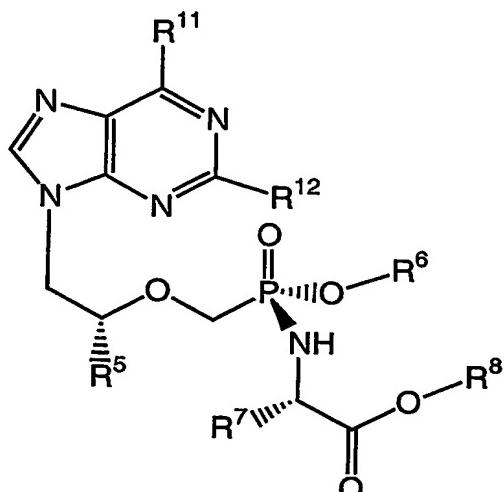
R is selected from H, C₁—C₁₈ alkyl, C₁—C₁₈ substituted alkyl, C₂—C₁₈ alkenyl, C₂—C₁₈ substituted alkenyl, C₂—C₁₈ alkynyl, C₂—C₁₈ substituted alkynyl, C₆—C₂₀ aryl, C₆—C₂₀ substituted aryl, C₂—C₂₀ heterocycle, C₂—C₂₀ substituted heterocycle, phosphonate, phosphophosphonate, diphosphophosphonate, phosphate, diphosphate, triphosphate, polyethyleneoxy, and a prodrug moiety.

10. The method according to claim 9 wherein the combination comprises a physiologically functional derivative of emtricitabine which is (2*R*, 5*S*, cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1*H*)-pyrimidin-2-one (3TC).

25 11. The method according to claim 1 wherein the combination comprises a physiologically functional derivative of emtricitabine which is a racemic mixture of the enantiomers (2*R*, 5*S*, cis)-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-

(1*H*)-pyrimidin-2-one and (2*S*, 5*R*, cis)-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1*H*)-pyrimidin-2-one.

12. The method according to claim 1 wherein the combination comprises a physiologically functional derivative of GS-7340 which has the structure:



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wherein R⁵ is H or CH₃; R⁶ and R⁸ are independently selected from H, C₁-C₆ alkyl, C₁-C₆ substituted alkyl, C₆-C₂₀ aryl, C₆-C₂₀ substituted aryl, C₆-C₂₀ arylalkyl, and C₆-C₂₀ substituted arylalkyl; R⁷ is the side chain of any naturally-occurring or pharmaceutically acceptable amino acid and where if the side chain comprises

10 carboxyl, the carboxyl group is optionally esterified with an alkyl or aryl group; R¹¹ is amino, alkylamino, oxo, or dialkylamino; and R¹² is amino or H; or a pharmaceutically acceptable salt or solvate thereof.

13. The method according to claim 12 wherein R⁷ is H, CH₃ or CH(CH₃)₂.

14. The method according to claim 12 wherein R⁶ is phenyl.

15 15. The method according to claim 12 wherein R⁸ is CH₃, CH₂CH₃, or CH(CH₃)₂.

16. The method according to claim 1 wherein GS-7340 or a physiologically functional derivative thereof, and emtricitabine or a physiologically functional derivative thereof are administered sequentially.

20 17. The method according to claim 1 wherein the combination is administered as a single combined formulation.

18. The method according to claim 17 wherein the single combined formulation is administered once per day to an infected human.

19. The method according to claim 1 in which said animal is a human.

20. The method according to claim 1 wherein the combination further
5 comprises a third active ingredient selected from a protease inhibitor (PI), a nucleoside reverse transcriptase inhibitor (NRTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), and an integrase inhibitor.

21. The method according to claim 20 wherein the third active ingredient is tenofovir disoproxil fumarate.

10 22. The method according to claim 1 wherein the combination further comprises a pharmaceutically acceptable glidant selected from silicon dioxide, powdered cellulose, microcrystalline cellulose, a metallic stearate, sodium aluminosilicate, sodium benzoate, calcium carbonate, calcium silicate, corn starch, magnesium carbonate, asbestos free talc, stearowet C, starch, starch 1500, magnesium 15 lauryl sulfate, magnesium oxide, and combinations thereof.

23. The method according to claim 22 wherein the metallic stearate is selected from calcium stearate, magnesium stearate, zinc stearate, and combinations thereof.

24. A pharmaceutical formulation comprising 9-[*R*-2-[(*S*)-[(*S*)-1-
20 (isopropoxycarbonyl)ethyl]amino]-phenoxyphosphinyl]methoxy]propyl]adenine (GS-7340) or a physiologically functional derivative thereof and (2*R*, 5*S*, cis)-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1*H*)-pyrimidin-2-one (emtricitabine) or a physiologically functional derivative thereof.

25. The pharmaceutical formulation according to claim 24 further comprising one or more pharmaceutically acceptable carriers or excipients.

26. The pharmaceutical formulation according to claim 25 wherein the pharmaceutically acceptable carriers or excipients are selected from pregelatinized starch, croscarmellose sodium, povidone, lactose monohydrate, microcrystalline cellulose, and magnesium stearate; and combinations thereof.

27. The pharmaceutical formulation according to claim 24 wherein GS-7340 or a physiologically functional derivative thereof and emtricitabine or a physiologically functional derivative thereof are present in a ratio of 1:50 to 50:1 by weight.

5 28. The pharmaceutical formulation according to claim 24 wherein GS-7340 or a physiologically functional derivative thereof and emtricitabine or a physiologically functional derivative thereof are present in a ratio of 1:10 to 10:1 by weight.

29. The pharmaceutical formulation according to claim 24 in unit dosage form.

10 30. The pharmaceutical formulation according to claim 29 wherein GS-7340 or a physiologically functional derivative thereof and emtricitabine or a physiologically functional derivative thereof are each and individually present in an amount from 100 mg to 1000 mg per unit dosage form.

31. The pharmaceutical formulation according to claim 24 comprising GS-7340 and emtricitabine.

15 32. The pharmaceutical formulation according to claim 31 comprising about 150 mg of GS-7340 and about 200 mg of emtricitabine.

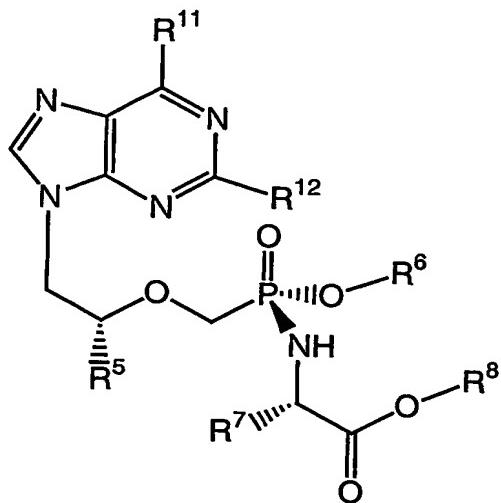
33. The pharmaceutical formulation according to claim 24 suitable for oral administration.

20 34. The pharmaceutical formulation according to claim 30 in the form of a tablet or capsule.

35. The pharmaceutical formulation according to claim 30 suitable for administration once per day to an infected human.

25 36. The pharmaceutical formulation according to claim 24 comprising a physiologically functional derivative of emtricitabine which is (2R, 5S, cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one (3TC).

37. The pharmaceutical formulation according to claim 24 comprising a physiologically functional derivative of GS-7340 which has the structure:



wherein R⁵ is H or CH₃; R⁶ and R⁸ are independently selected from H, C₁—C₆ alkyl, C₁—C₆ substituted alkyl, C₆—C₂₀ aryl, C₆—C₂₀ substituted aryl, C₆—C₂₀ arylalkyl, and C₆—C₂₀ substituted arylalkyl; R⁷ is the side chain of any naturally-occurring or

- 5 pharmaceutically acceptable amino acid and where if the side chain comprises carboxyl, the carboxyl group is optionally esterified with an alkyl or aryl group; R¹¹ is amino, alkylamino, oxo, or dialkylamino; and R¹² is amino or H;
or a pharmaceutically acceptable salt or solvate thereof.

38. The pharmaceutical formulation according to claim 37 wherein R⁷ is H,

- 10 CH₃ or CH(CH₃)₂.

39. The pharmaceutical formulation according to claim 37 wherein R⁶ is phenyl.

40. The pharmaceutical formulation according to claim 37 wherein R⁸ is CH₃, CH₂CH₃, or CH(CH₃)₂.

- 15 41. A patient pack comprising at least one active ingredient selected from 9-[R-2-[[*(S*)-[(*S*)-1-(isopropoxycarbonyl)ethyl]amino]-phenoxypyrophosphinyl]methoxy]propyl]adenine (GS-7340) and (2*R*,5*S*, cis)-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1*H*)-pyrimidin-2-one (emtricitabine), and an information insert containing directions on the use of GS-7340 and emtricitabine
20 together in combination.

42. The patient pack according to claim 41 comprising a co-formulated pill, tablet, caplet, or capsule of 100 to 1000 mg of GS-7340 and 100 to 1000 mg of emtricitabine.

5 43. The patient pack according to claim 41 comprising a co-formulated pill, tablet, caplet, or capsule of 300 mg of GS-7340 and 200 mg of emtricitabine.

44. The patient pack according to claim 41 comprising a separate pill, tablet, caplet, or capsule of 100 to 1000 mg of GS-7340 and 100 to 1000 mg of emtricitabine.

45. The patient pack according to claim 44 comprising a separate pill, tablet, caplet, or capsule of 150 mg of GS-7340 and 200 mg of emtricitabine.

10 46. A chemically stable combination of GS-7340 and emtricitabine.

47. The chemically stable combination of Claim 46 wherein the combination is a pharmaceutical dosage form.

48. The chemically stable combination of Claim 47 wherein the dosage form is oral.

15 49. The chemically stable combination of Claims 46-48 which further comprises a third antiviral agent.

50. The chemically stable combination of Claim 49 where in the third antiviral agent is an NNRTI or PI.

20 51. The chemically stable combination of Claim 50 wherein the third antiviral agent is a PI.

52. The chemically stable combination of Clam 50 wherein the third antiviral agent is an NNRTI.

53. The chemically stable combination of Claim 49 wherein the third antiviral agent is selected from Reyataz, Kaletra or Sustiva.

25 54. A chemically stable oral pharmaceutical dosage form comprising GS-7340 and emtricitabine.

55. A chemically stable oral pharmaceutical dosage form comprising GS-7340, emtricitabine and Reyataz.

56. A chemically stable oral pharmaceutical dosage form comprising GS-7340, emtricitabine and Kaletra.

57. A chemically stable oral pharmaceutical dosage form comprising GS-7340, emtricitabine and Sustiva.